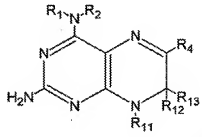
**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions and listings of claims in the application:

1-22. (Canceled)

23. (Currently Amended) A compound of formula I, stereoisomeric and tautomeric forms and mixtures ~~thereof in all ratios~~, and physiologically tolerated salts, ~~hydrates~~ and esters thereof:



(I)

wherein:

$R_1$ is chosen from hydrogen, ~~$(C_1$-$C_{20})$-alkyl, $(C_1$-$C_{20})$-alkenyl, $(C_1$-$C_{20})$-alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, aryl, alkylaryl, and arylalkyl, wherein the organic radicals may be substituted by at least one substituent~~ or lower alkyl,

$R_2$ is chosen from, independently of $R_1$, hydrogen, $(C_1$-$C_{20})$-alkyl, ~~$(C_1$-$C_{20})$-alkenyl, $(C_1$-$C_{20})$-alkynyl, cycloalkyl, cycloalkenyl,~~ and cycloalkylalkyl~~, aryl, alkylaryl, and arylalkyl, wherein the organic radicals may be substituted by at least one substituent, or~~

# Author Search

⇨ FILE HCAPLUS
FILE 'HCAPLUS' ENTERED AT 17:40:49 ON 25 AUG 2008
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FILE COVERS 1907 - 25 Aug 2008 VOL 149 ISS 9
FILE LAST UPDATED: 24 Aug 2008 (20080824/ED)

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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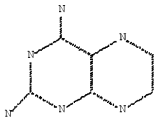
This file contains CAS Registry Numbers for easy and accurate substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

⇨ D STAT QUE L21
L3 STR

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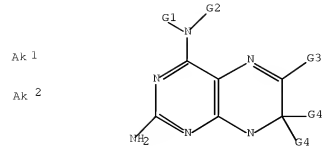
L13 STR




G1 H,[@1]
G2 H,Cb,[@2]
G3 OH,X,Ph,[@1],[@3]
G4 H,[@4]

Structure attributes must be viewed using STN Express query preparation.

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| L17 | 107 | SEA FILE=HCAPLUS ABB=ON AY<=2003 OR PY<=2003) | PLU=ON | L16 AND (PRY<=2003 OR | |
| L18 | 4 | SEA FILE=HCAPLUS ABB=ON | PLU=ON | DOBLHOFER R?/AU | |
| L19 | 56 | SEA FILE=HCAPLUS ABB=ON | PLU=ON | TEGTMEIER F?/AU | |
| L20 | 57 | SEA FILE=HCAPLUS ABB=ON | PLU=ON | (L18 OR L19) | |
| L21 | 3 | SEA FILE=HCAPLUS ABB=ON | PLU=ON | L20 AND L17 | |

⇨ D IBIB ED ABS HITSTR L21 1-3

L21 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:612291 HCAPLUS Full-text
DOCUMENT NUMBER: 143:153229
TITLE: Preparation of pharmaceutical compositions containing 4-amino-7,8-dihydropteridines and their use for the treatment of diseases which are caused by an increased nitric oxide level
INVENTOR(S): Doblhofer, Robert; Tegtmeier, Frank
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H., Germany
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005063752 | A1 | 20050714 | WO 2003-EP14970 | 20031230 ← |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,

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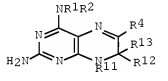
JP 2007525407 T 20070906 JP 2005-512684 20031230 ←
IN 2006DN03444 A 20070831 IN 2006-DN3444 20060615 ←
US 20080027062 A1 20080131 US 2007-584996 20070611 ←
PRIORITY APPLN. INFO.: WO 2003-EP14970 W 20031230 ←
OTHER SOURCE(S): CASREACT 143:153229; MARPAT 143:153229
ED Entered STN: 15 Jun 2005
GI



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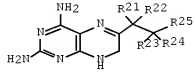

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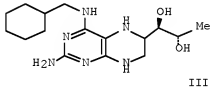

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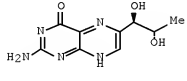


IV

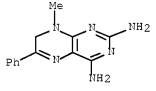
AB The present invention relates to the area of NO synthase inhibition and, more particularly, relates to novel 4-amino-7,8-dihydropteridines, e.g., I [R1, R2 = H, C1-20-alkyl, C1-20-alkenyl, C1-20-alkynyl, C3-8-cycloalkyl, cycloalkenyl, (cycloalkyl)alkyl, aryl, (c1-3-alkyl)aryl, etc.; NR1R2 = 3- to 8-membered ring (optionally containing 1 or 2 other heteroatoms - O, S, N); R4 = C1-20-alkyl, C1-20-alkenyl, C1-20-alkynyl, C3-8-cycloalkyl, cycloalkenyl, (cycloalkyl)alkyl, aryl, (C1-3-alkyl)aryl, etc.; R6, R7 = F, Cl, I, Br, O-(C1-10-alkyl), Oph, OC(:O)(C1-10-alkyl), OC(:O)aryl, NR8R9, oxo, Ph, C(:O)(C1-5-alkyl), CF3, CN, CONR8R9, CO2H, C(:O)O-(C1-5-alkyl), C(:O)O-aryl, S(O)n-(C1-5-alkyl), SO2NR8R9; R8 = H, C1-20-alkyl; R9 = H, C1-20-alkyl, aryl (preferably Ph); R11 = H, C1-20-alkyl, aryl, CO-alkyl, CO-aryl; R12, R13 = H, C1-10-alkyl, aryl, O-(C1-10-alkyl), Oph, OC(:O)-C1-10-alkyl, OC(:O)-aryl, NR8R9, Ph, C(:O)-C1-10-alkyl, CF3, CN, CONR8R9, CO2H, etc.; aryl = (un)substituted Ph, naphthyl, heteroaryl; heteroaryl = 5- to 7-membered ring (optionally containing an addnl. Heteroatom - O, N, S); n = 0 - 2], or their pharmaceutically acceptable acid addition salts, hydrates and esters, pharmaceutical compns. Containing said compds., and the use of said compds. In the treatment of a disorder characterized by a disturbed nitric oxide level. The patent particularly excludes compds. II [R21, R22, R23, R24 = ; R25 = H, Me, CH2OH, CHO, (un)branched C1-9-alkyl, (CHOH)nY, (CHOH)n(CH2)mW; Y = H, C1-9-alkyl; W = H, OH; n, m = 1 - 20]. Thus, 4-[(Cyclohexylmethyl)amino]-5,6,7,8-tetrahydrobiopterin (III) was prepared from biopterin (IV) via acetylation with Ac2O in pyridine, reaction with PhCH2CH2OH in dioxane containing Ph3P, amination with (cyclohexylmethyl)amine in dioxane, and hydrogenation in CF2CO4H containing catalytic PtO2. The in vivo stability

[t1/2 = << 5 min. (tetrahydro); t1/2 = 48 min. (dihydro)] and NO release inhibitor activity for I was determined

IT 858127-54-5P, 2,4-Diamino-8-methyl-6-phenyl-7,8-dihydropteridine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pharmaceutical compns. Containing 4-amino-7,8-dihydropteridines
and their use for the treatment of diseases which are caused by an increased nitric oxide level)

RN 858127-54-5 HCAPLUS

CN 2,4-Pteridinediamine, 7,8-dihydro-8-methyl-6-phenyl- (CA INDEX NAME)




REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:371070 HCAPLUS Full-text

DOCUMENT NUMBER: 142:404279

TITLE: Use of pteridine derivatives for the treatment of increased intracranial pressure and secondary ischemia

INVENTOR(S): Doblhofer, Robert; Tegtmeier, Frank

PATENT ASSIGNEE(S): Vasopharm Biotech GmbH, Germany

SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2005037286 | A1 | 20050428 | WO 2003-EP3096 | 20030325 ← |
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| CA 2519919 | A1 | 20041007 | CA 2003-2519919 | 20031008 ← |
| WO 2004084906 | A1 | 20041007 | WO 2003-EP11138 | 20031008 ← |
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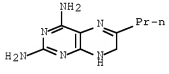
| AU 2003293607 | A1 | 20041018 | AU 2003-293607 | 20031008 ← |
| EP 1605947 | A1 | 20051221 | EP 2003-788945 | 20031008 ← |

EP 1605947 B1 20060802
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
CN 1758913 A 20060412 CN 2003-80110211 20031008 ←
JP 2006514965 T 20060518 JP 2004-569858 20031008 ←
AT 334681 T 20060815 AT 2003-788945 20031008 ←
ES 2270151 T3 20070401 ES 2003-788945 20031008 ←
MX 2005PA09491 A 20060222 MX 2005-PA9491 20050906 ←
US 20070032498 A1 20070208 US 2005-549200 20050916 ←
PRIORITY APPLN. INFO.: WO 2003-EP3096 A 20030325 ←
WO 2003-EP11138 W 20031008 ←

OTHER SOURCE(S): MARPAT 142:404279
ED Entered STN: 29 Apr 2005
AB The invention discloses the use of pteridine _erives. For treating increased intracranial pressure and/or secondary ischemia. Compound preparation is included.
IT 50691-64-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pteridine _erives. For treatment of increased intracranial pressure and secondary ischemia)
RN 50691-64-0 HCAPLUS
CN 2,4-Pteridinediamine, 1,7-dihydro-6-propyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:817714 HCAPLUS Full-text
DOCUMENT NUMBER: 141:307610
TITLE: Use of pteridine derivatives for the treatment of increased intracranial pressure, secondary ischemia, and disorders associated with an increased level of cytotoxic reactive oxygen species
INVENTOR(S): Dobihofer, Robert; Tegtmeier, Frank
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H., Germany
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2004084906 | A1 | 20041007 | WO 2003-EP11138 | 20031008 ← |

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LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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| W: US | | | | | |
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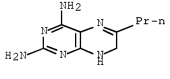
| AU 2003293607 | A1 | 20041018 | AU 2003-293607 | 20031008 | ← |
| EP 1605947 | A1 | 20051221 | EP 2003-788945 | 20031008 | ← |
| EP 1605947 | B1 | 20060802 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | | |
| JP 2006514965 | T | 20060518 | JP 2004-569858 | 20031008 | ← |
| MX 2005PA09491 | A | 20060222 | MX 2005-PA9491 | 20050906 | ← |
| US 20070032498 | A1 | 20070208 | US 2005-549200 | 20050916 | ← |
| PRIORITY APPLN. INFO.: | | | WO 2003-EP3096 A | 20030325 | ← |
| | | | WO 2003-EP11138 W | 20031008 | ← |

OTHER SOURCE(S): MARPAT 141:307610
ED Entered STN: 07 Oct 2004
AB The present invention relates to the use of pteridine _erives. For the treatment of increased intracranial pressure, secondary ischemia, and disorders associated with an increased level of cytotoxic reactive oxygen species. H4-aminobiopterin (preparation given) caused a clear concentration dependent contraction of both rat basilar arteries and middle cerebral arteries.
IT 50691-64-0
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pteridine _erives. For treatment of increased intracranial pressure, secondary ischemia, and disorders associated with increased levels of cytotoxic reactive oxygen species)
RN 50691-64-0 HCAPLUS
CN 2,4-Pteridinediamine, 1,7-dihydro-6-propyl- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE COVERS 1907 - 25 Aug 2008  VOL 149 ISS 9
FILE LAST UPDATED: 24 Aug 2008  (20080824/ED)

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2008.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
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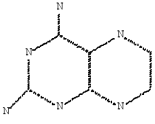


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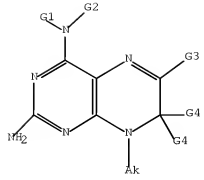


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G3 OH,X,Ph,[@1],[@3]
G4 H,[@4]

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L40            3 L30 NOT L21

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FILE LAST UPDATED:           22 AUG 2008   <20080822/UP>
MOST RECENT UPDATE:            200854      <200854/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
>>> Now containing more than 1.1 million chemical structures in DCR <<<

>>> IPC Reform backfile reclassifications have been loaded to the end of
    June 2008. No update date (UP) has been created for the
    reclassified documents, but they can be identified by
    20060101/UPIC and 20061231/UPIC, 20070601/UPIC, 20071001/UPIC,
    20071130/UPIC, 20080401/UPIC and 20080701/UPIC.
    ECLA reclassifications to June and US national classifications to
    the end of April 2008 have also been loaded. Update dates
    20080401 and 20080701/UPEC and /UPNC have been assigned to these. <<<

FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomsonreuters.com/support/patents/coverage/latestupdates/

EXPLORE DERWENT WORLD PATENTS INDEX IN STN ANAVIST, VERSION 2.0:
http://www.stn-international.com/archive/presentations/DWPIAnaVist2_0710.pdf

>>> HELP for European Patent Classifications see HELP ECLA, HELP ICO <<<

>>> Please note that the COPYRIGHT notification has changed <<<
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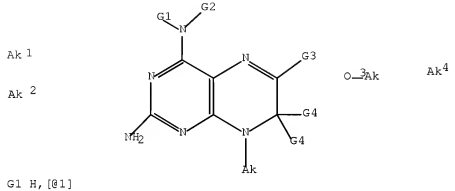
L27 STR

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G2 H,Cb,[@2]
G3 OH,X,Ph,[@1],[@3]
G4 H,[@4]

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SEARCH TIME: 00.00.04

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FILE LAST UPDATED ON April 1, 2008

FILE COVERS 1771 TO 2008.
*** FILE CONTAINS 10.322,808 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
separate documents and can not be searched together in one query.
Reaction data for BEILSTEIN compounds may be displayed
immediately with the display codes PRE (preparations) and REA
(reactions). A substance answer set retrieved after the search
for a chemical name, a compounds with available reaction
information by combining with PRE/FA, REA/FA or more generally
with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
between a BEILSTEIN compound and belonging reactions. For mo
detailed reaction searches BRNs can be searched as reaction
partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

**********

```
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE   *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE          *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                        *
* FOR PRICE INFORMATION SEE HELP COST                                *
**********************************************************************

>>> Price change as of January 1st, 2008: Connect Time and Structure
    Search fees re-introduced. See NEWS and HELP COST <<<

=> D STAT QUE L37
L3                STR
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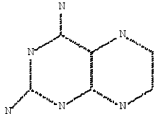

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Structure attributes must be viewed using STN Express query preparation.
L5          4906 SEA FILE=REGISTRY SSS FUL L3
L27               STR
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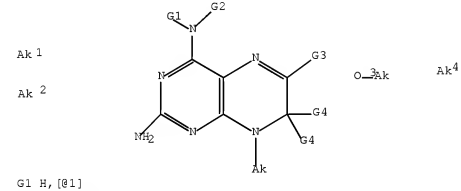


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 G1 H,[@1]
 G2 H,Cb,[@2]
 G3 OH,X,Ph,[@1],[@3]
 G4 H,[@4]


Structure attributes must be viewed using STN Express query preparation.
L29               6 SEA FILE=REGISTRY SUB=L5 SSS FUL L27
L34               5 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L29
L35               1 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L34 AND BABSAN/FA
L37               4 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L34 NOT L35


=> FILE BABS
```

```
FILE 'BABS' ENTERED AT 17:41:58 ON 25 AUG 2008
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licensed to Beilstein Chemiedaten & Software GmbH and MDL Information Systems GmbH

FILE LAST UPDATED: 14 JUL 2008       <20080714/UP>
FILE COVERS 1980 TO DATE.

=> D STAT QUE L36
L36           1 SEA FILE=BABS ABB=ON  PLU=ON  5617307/BABSAN


=> FILE MARPAT
FILE 'MARPAT' ENTERED AT 17:42:10 ON 25 AUG 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE CONTENT: 1961-PRESENT VOL 149 ISS 7 (20080822/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US  20080167493 10 JUL 2008
DE 102007009957 03 JUL 2008
EP      1939208 02 JUL 2008
JP   2008159496 10 JUL 2008
WO   2008086729 24 JUL 2008
GB      2444641 11 JUN 2008
FR      2910897 04 JUL 2008
RU      2330028 27 JUL 2008
CA      2615024 14 JUN 2008

Expanded G-group definition display now available.

Effective December 15th the iteration and answer limits in MARPAT
have increased from 100,000 to 200,000 for both on-line and batch
searches.  For more information on MARPAT search limits, type HELP
SLIMITS at an arrow prompt.

=> D STAT QUE L39
L27             STR
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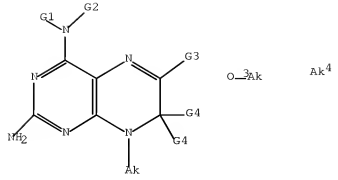


G1 H,[@1]
G2 H,Cb,[@2]
G3 OH,X,Ph,[@1],[@3]
G4 H,[@4]

Structure attributes must be viewed using STN Express query preparation.
L39 11 SEA FILE=MARPAT SSS FUL L27

100.0% PROCESSED 3228 ITERATIONS 11 ANSWERS
SEARCH TIME: 00.00.02

=> DUP REM L40 L32 L37 L36 L39
L32 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'BEILSTEIN'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 17:42:30 ON 25 AUG 2008
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FILE 'MARPAT' ENTERED AT 17:42:30 ON 25 AUG 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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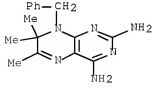
COPYRIGHT (C) 2008 American Chemical Society (ACS)
PROCESSING COMPLETED FOR L40
PROCESSING COMPLETED FOR L32
PROCESSING COMPLETED FOR L37
PROCESSING COMPLETED FOR L36
PROCESSING COMPLETED FOR L39
L41 18 DUP REM L40 L32 L37 L36 L39 (1 DUPLICATE REMOVED)
ANSWERS '1-3' FROM FILE HCAPLUS
ANSWERS '4-7' FROM FILE BEILSTEIN
ANSWERS '8-18' FROM FILE MARPAT

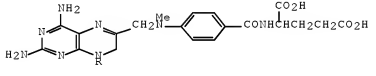
=> D IBIB ED ABS HITSTR 1-3; D IDE ALLREF 4-7; D IBIB AB QHIT 8-18

L41 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 1986:207023 HCAPLUS Full-text
DOCUMENT NUMBER: 104:207023
ORIGINAL REFERENCE NO.: 104:32801a,32804a
TITLE: Specific inhibitors in vitamin biosynthesis. Part 9. Reactions of 7,7-dialkyl-7,8-dihydropteridines of use in the synthesis of potential inhibitors of tetrahydrofolate biosynthesis
AUTHOR(S): Al-Hassan, Saiba S.; Cameron, Robert; Nicholson, Sydney H.; Robinson, David H.; Suckling, Colin J.; Wood, Hamish C. S.
CORPORATE SOURCE: Dep. Pure Appl. Chem., Univ. Strathclyde, Glasgow, G1 1XL, UK
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1985), (10), 2145-50
CODEN: JCPRB4; ISSN: 0300-922X
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 104:207023
ED Entered STN: 14 Jun 1986
AB 7,7-Dialkyl-7,8-dihydropteridines which were modified on the pyrazine ring to yield compds. with inhibitory activity against 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase and dihydrofolate reductase. These enzymes lie along the pathway leading to the coenzyme tetrahydrofolate. 6-Me substituents showed typical reactivity of alkyl groups α- to a pyrazine N and underwent exchange of H for D under acidic and basic conditions; however, they failed to undergo clean bromination or aldol condensation. Autoxidn. of alkyl groups at this position provided ready access to pteridines substituted with carbonyl groups at C-6. 6-Formyl derivs. underwent Wittig-type reactions to yield 6-aralkylidene compds. that are potential inhibitors of dihydrofolate reductase. Alkylation of the anion of 2,4-diamino-7,8-dihydro-6,7,7-trimethylpteridine occurred at N-8 in low yield. The reduction of the blocked dihydropteridine system was readily accomplished using catalytic hydrogenation in a manner analogous to that used for normal pteridines.
IT 102223-19-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 102223-19-8 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6,7,7-trimethyl-8-(phenylmethyl)- (CA INDEX NAME)




L41 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1977:527210 HCAPLUS Full-text
DOCUMENT NUMBER: 87:127210

ORIGINAL REFERENCE NO.: 87:20125a,20128a
TITLE: Methotrexate analogs. 9. Synthesis and biological properties of some 8-alkyl-7,8-dihydro analogs
AUTHOR(S): Chaykovsky, Michael; Hirst, Margaret; Lazarus, Herbert; Martinelli, Jack E.; Kisliuk, Roy L.; Gaumont, Yvette
CORPORATE SOURCE: Sidney Farber Cancer Inst., Harvard Med. Sch., Boston, MA, USA
SOURCE: Journal of Medicinal Chemistry (1977), 20(10), 1323-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 87:127210
ED Entered STN: 12 May 1984
GI

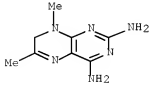


I, R=H
II, R=Me

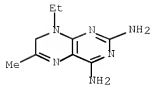
AB Eight title derivs. were prepared by direct alkylation of 7,8-dihydromethotrexate (I) [14009-31-5]. I and 8-methyl-7,8- dihydromethotrexate (II) [54820-64-3] were comparable to methotrexate (MTX) in their inhibition of Lactobacillus casei growth. I and all its derivs. were less inhibitory toward dihydrofolate reductase [9002-03-3] than MTX, but all were more inhibitory towared thymidylate synthetase [9031-61-2] from L. casei. I was about as active as MTX in vitro against CCRF-CEM human lymphoblastic cells, but was inactive against L1210 leukemia in mice. The 8-alkyl derivs. of I were much less toxic than I, and several derivs. had some in vivo activity against L1210 leukemia.

IT 54820-59-6P 54820-61-0P 54820-62-1P
54820-63-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

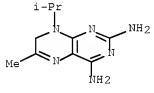
RN 54820-59-6 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6,8-dimethyl- (CA INDEX NAME)



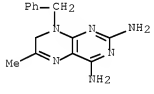
RN 54820-61-0 HCAPLUS
CN 2,4-Pteridinediamine, 8-ethyl-7,8-dihydro-6-methyl- (CA INDEX NAME)



RN 54820-62-1 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6-methyl-8-(1-methylethyl)- (CA INDEX NAME)



RN 54820-63-2 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6-methyl-8-(phenylmethyl)- (CA INDEX NAME)

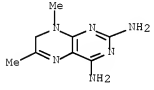


L41 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1975:86281 HCAPLUS Full-text
DOCUMENT NUMBER: 82:86281
ORIGINAL REFERENCE NO.: 82:13795a,13798a
TITLE: Direct N8-alkylation of 2,4-diamino-7,8-dihydropteridines. Preparation of 7,8-dihydro-8-methyl methotrexate
AUTHOR(S): Chaykovsky, Michael
CORPORATE SOURCE: Sidney Farber Cancer Cent., Harvard Med. Sch., Boston, MA, USA
SOURCE: Journal of Organic Chemistry (1975), 40(1), 145-146
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 82:86281
ED Entered STN: 12 May 1984
GI For diagram(s), see printed CA Issue.

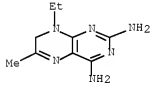
AB A method is described for the N8-alkylation of 2,4-diamino-7,8-dihydropteridines by reaction of these compds. with BuLi in Me2SO followed by treatment with an alkyl halide. 2,4-Diamino-7,8-dihydro-6- methylpteridine (I) was converted into the 8-Me, Et, CHMe2, and PhCH2 derivs. in yields of 71, 60, 24, and 80%, resp. The antitumor agent, methotrexate, was reduced with Na dithionite to the 7,8-dihydro derivative II, which was then methylated at N-8 in 50% yield. These compds. were prepared for chemotherapeutic evaluation.

IT 54820-59-6P 54820-61-0P 54820-62-1P
54820-63-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

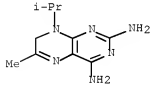
RN 54820-59-6 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6,8-dimethyl- (CA INDEX NAME)



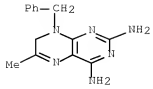
RN 54820-61-0 HCAPLUS
CN 2,4-Pteridinediamine, 8-ethyl-7,8-dihydro-6-methyl- (CA INDEX NAME)



RN 54820-62-1 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6-methyl-8-(1-methylethyl)- (CA INDEX NAME)

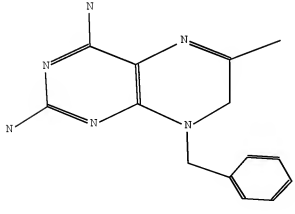


RN 54820-63-2 HCAPLUS
CN 2,4-Pteridinediamine, 7,8-dihydro-6-methyl-8-(phenylmethyl)- (CA INDEX NAME)




L41 ANSWER 4 OF 18 BEILSTEIN COPYRIGHT 2008 BEILSTEIN MDL on STN

| | |
|---|---|
| Beilstein Records (BRN): | 551214 |
| Beilstein Pref. RN (BPR): | 54820-63-2 |
| CAS Reg. No. (RN): | 54820-63-2 |
| Chemical Name (CN): | 8-benzyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |
| Autonom Name (AUN): | 8-benzyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |
| Molec. Formula (MF): | C14 H16 N6 |
| Molecular Weight (MW): | 268.32 |
| Lawson Number (LN): | 30708, 14140 |
| Compound Type (CTYPE): | heterocyclic |
| Constitution ID (CONSID): | 514022 |
| Tautomer ID (TAUTID): | 549847 |
| Beilstein Citation (BSO): | 5-26-17-00373 |
| Entry Date (DED): | 1988/11/28 |
| Update Date (DUPD): | 1995/11/15 |




Field Availability:

| Code | Name | Occurrence |
|---|---|---|
| BRN | Beilstein Records | 1 |

| | | |
|---|---|---|
| BPR | Beilstein Preferred RN | 1 |
| RN | CAS Registry Number | 1 |
| CN | Chemical Name | 1 |
| AUN | Autonomname | 1 |
| MF | Molecular Formula | 1 |
| FW | Formular Weight | 1 |
| LN | Lawson Number | 2 |
| CTYPE | Compound Type | 1 |
| CONSID | Constitution ID | 1 |
| TAUTID | Tautomer ID | 1 |
| BSO | Beilstein Citation | 1 |
| ED | Entry Date | 1 |
| UPD | Update Date | 1 |
| MP | Melting Point | 1 |
| UVS | UV and Visible Spectrum | 1 |

This substance also occurs in Reaction Documents:

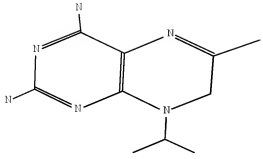
| Code | Name | Occurrence |
|---|---|---|
| RX | Reaction Documents | 1 |
| RXPRO | Substance is Reaction Product | 1 |

All References:
ALLREF

1. Chaykorsky et al., J.Med.Chem., CODEN: JMCMAR, 20, <1977>, 1323,1326
2. Chaykovsky, J.Org.Chem., CODEN: JOCEAH, 40, <1975>, 145

L41 ANSWER 5 OF 18 BEILSTEIN COPYRIGHT 2008 BEILSTEIN MDL on STN

| | |
|---|---|
| Beilstein Records (BRN): | 532168 |
| Beilstein Pref. RN (BPR): | 54820-62-1 |
| CAS Reg. No. (RN): | 54820-62-1 |
| Chemical Name (CN): | 8-isopropyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |
| Autonom Name (AUN): | 8-isopropyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |
| Molec. Formula (MF): | C10 H16 N6 |
| Molecular Weight (MW): | 220.28 |
| Lawson Number (LN): | 30708, 2836 |
| Compound Type (CTYPE): | heterocyclic |
| Constitution ID (CONSID): | 494130 |
| Tautomer ID (TAUTID): | 541142 |
| Beilstein Citation (BSO): | 5-26-17-00373 |
| Entry Date (DED): | 1988/11/28 |
| Update Date (DUPD): | 1995/11/15 |



Field Availability:

| Code | Name | Occurrence |
|---|---|---|
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| BPR | Beilstein Preferred RN | 1 |
| RN | CAS Registry Number | 1 |
| CN | Chemical Name | 1 |
| AUN | Autonomname | 1 |
| MF | Molecular Formula | 1 |
| FW | Formular Weight | 1 |
| LN | Lawson Number | 2 |
| CTYPE | Compound Type | 1 |
| CONSID | Constitution ID | 1 |
| TAUTID | Tautomer ID | 1 |
| BSO | Beilstein Citation | 1 |
| ED | Entry Date | 1 |
| UPD | Update Date | 1 |
| MP | Melting Point | 1 |
| UVS | UV and Visible Spectrum | 1 |

This substance also occurs in Reaction Documents:

| Code | Name | Occurrence |
|---|---|---|
| RX | Reaction Documents | 1 |
| RXPRO | Substance is Reaction Product | 1 |

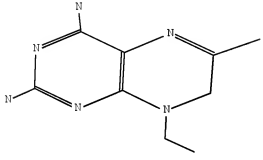
All References:
ALLREF

1. Chaykorsky et al., J.Med.Chem., CODEN: JMCMAR, 20, <1977>, 1323,1326
2. Chaykovsky, J.Org.Chem., CODEN: JOCEAH, 40, <1975>, 145

L41 ANSWER 6 OF 18 BEILSTEIN COPYRIGHT 2008 BEILSTEIN MDL on STN

| | |
|---|---|
| Beilstein Records (BRN): | 531116 |
| Beilstein Pref. RN (BPR): | 54820-61-0 |
| CAS Reg. No. (RN): | 54820-61-0 |
| Chemical Name (CN): | 8-ethyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |
| Autonom Name (AUN): | 8-ethyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine |

| | |
|---|---|
| Molec. Formula (MF): | C9 H14 N6 |
| Molecular Weight (MW): | 206.25 |
| Lawson Number (LN): | 30708, 2826 |
| Compound Type (CTYPE): | heterocyclic |
| Constitution ID (CONSID): | 492436 |
| Tautomer ID (TAUTID): | 540920 |
| Beilstein Citation (BSO): | 5-26-17-00373 |
| Entry Date (DED): | 1988/11/28 |
| Update Date (DUPD): | 1995/11/15 |



Field Availability:

| Code | Name | Occurrence |
|---|---|---|
| BRN | Beilstein Records | 1 |
| BPR | Beilstein Preferred RN | 1 |
| RN | CAS Registry Number | 1 |
| CN | Chemical Name | 1 |
| AUN | Autonomname | 1 |
| MF | Molecular Formula | 1 |
| FW | Formular Weight | 1 |
| LN | Lawson Number | 2 |
| CTYPE | Compound Type | 1 |
| CONSID | Constitution ID | 1 |
| TAUTID | Tautomer ID | 1 |
| BSO | Beilstein Citation | 1 |
| ED | Entry Date | 1 |
| UPD | Update Date | 1 |
| MP | Melting Point | 1 |
| UVS | UV and Visible Spectrum | 1 |

This substance also occurs in Reaction Documents:

| Code | Name | Occurrence |
|---|---|---|
| RX | Reaction Documents | 1 |
| RXPRO | Substance is Reaction Product | 1 |

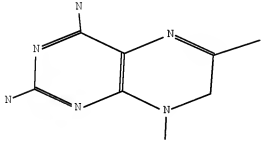
All References:
ALLREF

1. Chaykorsky et al., J.Med.Chem., CODEN: JMCMAR, 20, <1977>, 1323,1326

2. Chaykovsky, J.Org.Chem., CODEN: JOCEAH, 40, <1975>, 145

L41 ANSWER 7 OF 18 BEILSTEIN COPYRIGHT 2008 BEILSTEIN MDL on STN

| | |
|---|---|
| Beilstein Records (BRN): | 525714 |
| Beilstein Pref. RN (BPR): | 54820-59-6 |
| CAS Reg. No. (RN): | 54820-59-6 |
| Chemical Name (CN): | 6,8-dimethyl-7,8-dihydro-pteridine-2,4-diamine |
| Autonom Name (AUN): | 6,8-dimethyl-7,8-dihydro-pteridine-2,4-diamine |
| Molec. Formula (MF): | C8 H12 N6 |
| Molecular Weight (MW): | 192.22 |
| Lawson Number (LN): | 30708, 2817 |
| Compound Type (CTYPE): | heterocyclic |
| Constitution ID (CONSID): | 487558 |
| Tautomer ID (TAUTID): | 538046 |
| Beilstein Citation (BSO): | 5-26-17-00372 |
| Entry Date (DED): | 1988/11/28 |
| Update Date (DUPD): | 1995/11/15 |



Field Availability:

| Code | Name | Occurrence |
|---|---|---|
| BRN | Beilstein Records | 1 |
| BPR | Beilstein Preferred RN | 1 |
| RN | CAS Registry Number | 1 |
| CN | Chemical Name | 1 |
| AUN | Autonomname | 1 |
| MF | Molecular Formula | 1 |
| FW | Formular Weight | 1 |
| LN | Lawson Number | 2 |
| CTYPE | Compound Type | 1 |
| CONSID | Constitution ID | 1 |
| TAUTID | Tautomer ID | 1 |
| BSO | Beilstein Citation | 1 |
| ED | Entry Date | 1 |
| UPD | Update Date | 1 |
| MP | Melting Point | 1 |
| NMR | Nuclear Magnetic Resonance | 1 |
| UVS | UV and Visible Spectrum | 1 |

This substance also occurs in Reaction Documents:

| Code | Name | Occurrence |
|---|---|---|
| RX | Reaction Documents | 1 |
| RXPRO | Substance is Reaction Product | 1 |

All References:
ALLREF


1. Chaykorsky et al., J.Med.Chem., CODEN: JMCMAR, 20, <1977>, 1323,1326
2. Chaykovsky, J.Org.Chem., CODEN: JOCEAH, 40, <1975>, 145


L41 ANSWER 8 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 148:517556 MARPAT Full-text
TITLE: Heteroaryl compounds, compositions thereof, preparation and methods of treatment therewith
INVENTOR(S): Mortensen, Deborah Sue; Mederos, Maria Mercedes Delgado; Sapienza, John Joseph; Albers, Ronald J.; Lee, Branden G.; Harris, Roy Leonard., III; Shevlin, Graziella Isabel; Huang, Dehua; Schwarz, Kimberly Lyn; Packard, Garrick K.; Parnes, Jason Simon; Papa, Patrick William; Tehrani, Lida Radnia; Perrin-Ninkovic, Sophie
PATENT ASSIGNEE(S): Signal Pharmaceuticals, LLC, USA
SOURCE: PCT Int. Appl., 299pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2008051493 | A2 | 20080502 | WO 2007-US22374 | 20071018 |
| WO 2008051493 | A3 | 20080703 | | |

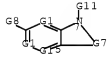
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: US 2006-853166P 20061019


AB Provided herein are heteroaryl compds. having the following structure I, compns. comprising an effective amount of a heteroaryl compound and methods for treating or preventing cancer, inflammatory conditions, immunol. conditions, metabolic conditions and conditions treatable or preventable by inhibition of a kinase pathway comprising administering an effective amount of a heteroaryl compound to a patient in need thereof. Compds. of formula I wherein X, Y and Z are independently N and CR3, wherein at least one of X, Y

and Z is N and at least one of X, Y and Z is CR3; A-B-Q taken together to form CHR4CONH, COCHR4NH, CONH, CH2CO2, COCH2O, CO2, and CONHR3; L is a bond, NH and O; R1 and R2 are independently H, (un)substituted C1-8 alkyl, (un)substituted C2-8 alkenyl, (un)substituted (hetero)aryl, and (un)substituted (hetero)cycloalkyl; R3 is H, (un)substituted C1-8 alkyl, (un)substituted C2-8 alkenyl, (un)substituted (hetero)aryl, (un)substituted (hetero)cycloalkyl, NHR4 and N(R4)2; R4 is (un)substituted C1-8 alkyl, (un)substituted C2-8 alkenyl, (un)substituted (hetero)aryl, and (un)substituted (hetero)cycloalkyl; and their pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by debenzylation of [3-amino-6-(quinolin-5-yl)pyrazin-2-yl](4- methoxybenzyl)amine; the resulting 5-(quinolin-5-yl)pyrazin-2,3-diamine underwent cyclization with urea to give compound II. All the invention compds. were evaluated for their protein kinase inhibitory activity. From the assay, it was determined that compound II exhibited IC50 values of 0.1-5 μM against mTOR, and >30 μM against PKCθ.

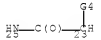
MSTR 1




G1 = N / 13


G2 = 15


G3 = NH
G7 = 25-5 23-7



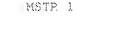

G8 = NH2
G11 = alkyl <containing 1-8 C> (opt. substd.)
Patent location: claim 1
Note: or pharmaceutically acceptable salts
Note: substitution is restricted

L41 ANSWER 9 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:221126 MARPAT Full-text
TITLE: Dihydropteridinones in the treatment of respiratory diseases
INVENTOR(S): Maier, Udo; Kalkbrenner, Frank; Breitfelder, Steffen; Buettner, Frank; Grauert, Matthias; Hoffmann, Matthias
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma Gmbh & Co.Kg
SOURCE: PCT Int. Appl., 93pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2007014838 | A1 | 20070208 | WO 2006-EP64305 | 20060717 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| CA 2617589 | A1 | 20070208 | CA 2006-2617589 | 20060717 |
| EP 1915155 | A1 | 20080430 | EP 2006-777805 | 20060717 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR | | | | |
| US 20070043055 | A1 | 20070222 | US 2006-458217 | 20060718 |
| PRIORITY APPLN. INFO.: | | | EP 2005-107149 | 20050803 |
| | | | WO 2006-EP64305 | 20060717 |

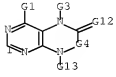
AB The invention discloses the use of dihydropteridinones I [X = O, S; R1 = H, NH2, XH, etc.; R2 = H, CHO, XH, etc.; R3, R4 = (un)substituted C1-10 alkyl, C2-10 alkenyl, etc.; R5 = H, (un)substituted C1-10 alkyl, etc.; R6 = (un)substituted (hetero)aryl; R7 = H, COX-C1-4 alkyl; R8 = H, (un)substituted C1-4 alkyl, etc.] for the preparation of a medicament for the treatment of respiratory diseases.

MSTP 1




G1 = NH2
G4 = 14

G12 = O
G13 = alkyl <containing 1-10 C> (opt. substd.)
G15 = NH
G18 = 1




Patent location: claim 1
Note: and pharmacologically acceptable acid addition salts
Note: also incorporates claims 10 and 12
Note: substitution is restricted
Stereochemistry: and tautomers, racemates, enantiomers, diastereomers and mixtures

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 10 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 143:153229 MARPAT Full-text
TITLE: Preparation of pharmaceutical compositions containing 4-amino-7,8-dihydropteridines and their use for the treatment of diseases which are caused by an increased nitric oxide level
INVENTOR(S): Doblhofer, Robert; Tegtmeier, Frank
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H., Germany
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005063752 | A1 | 20050714 | WO 2003-EP14970 | 20031230 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2552195 | A1 | 20050714 | CA 2003-2552195 | 20031230 |
| AU 2003290127 | A1 | 20050721 | AU 2003-290127 | 20031230 |
| EP 1699793 | A1 | 20060913 | EP 2003-782489 | 20031230 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |

IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK

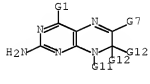
| | | | | | |
|---|---|---|---|---|---|
| JP 2007525407 | T | 20070906 | JP 2005-512684 | 20031230 |
| IN 2006DN03444 | A | 20070831 | IN 2006-DN3444 | 20060615 |
| US 20080027062 | A1 | 20080131 | US 2007-584996 | 20070611 |

PRIORITY APPLN. INFO.: WO 2003-EP14970 20031230

OTHER SOURCE(S): CASREACT 143:153229

AB The present invention relates to the area of NO synthase inhibition and, more particularly, relates to novel 4-amino-7,8-dihydropteridines, e.g., I [R1, R2 = H, C1-20-alkyl, C1-20-alkenyl, C1-20-alkynyl, C3-8-cycloalkyl, cycloalkenyl, (cycloalkyl)alkyl, aryl, (c1-3-alkyl)aryl, etc.; NR1R2 = 3- to 8-membered ring (optionally containing 1 or 2 other heteroatoms - O, S, N); R4 = C1-20-alkyl, C1-20-alkenyl, C1-20-alkynyl, C3-8-cycloalkyl, cycloalkenyl, (cycloalkyl)alkyl, aryl, (C1-3-alkyl)aryl, etc.; R6, R7 = F, Cl, I, Br, O-(C1-10-alkyl), OPh, OC(:O)(C1-10-alkyl), OC(:O)aryl, NR8R9, oxo, Ph, C(:O)(C1-5-alkyl), CF3, CN, CONR8R9, CO2H, C(:O)O-(C1-5-alkyl), C(:O)O-aryl, S(O)n-(C1-5-alkyl), SO2NR8R9; R8 = H, C1-20-alkyl; R9 = H, C1-20-alkyl, aryl (preferably Ph); R11 = H, C1-20-alkyl, aryl, CO-alkyl, CO-aryl; R12, R13 = H, C1-10-alkyl, aryl, O-(C1-10-alkyl), OPh, OC(:O)-C1-10-alkyl, OC(:O)-aryl, NR8R9, Ph, C(:O)-C1-10-alkyl, CF3, CN, CONR8R9, CO2H, etc.; aryl = (un)substituted Ph, naphthyl, heteroaryl; heteroaryl = 5- to 7-membered ring (optionally containing an addnl. heteroatom - O, N, S); n = 0 - 2], or their pharmaceutically acceptable acid addition salts, hydrates and esters, pharmaceutical compns. containing said compds., and the use of said compds. in the treatment of a disorder characterized by a disturbed nitric oxide level. The patent particularly excludes compds. II [R21, R22, R23, R24 = ; R25 = H, Me, CH2OH, CHO, (un)branched C1-9-alkyl, (CHOH)nY, (CHOH)n(CH2)mW; Y = H, C1-9-alkyl; W = H, OH; n, m = 1 - 20]. Thus, 4-[(Cyclohexylmethyl)amino]-5,6,7,8-tetrahydrobiopterin (III) was prepared from biopterin (IV) via acetylation with Ac2O in pyridine, reaction with PhCH2CH2OH in dioxane containing Ph3P, amination with (cyclohexylmethyl)amine in dioxane, and hydrogenation in CF2CO4H containing catalytic PtO2. The in vivo stability [t1/2 = << 5 min. (tetrahydro); t1/2 = 48 min. (dihydro)] and NO release inhibitor activity for I was determined

MSTR 1




G1 = NH2
G7 = Ph (opt. substd. by alkyl <containing 1-20 C>)
G11 = alkyl <containing 1-20 C> (opt. substd.)

| | |
|---|---|
| Patent location: | claim 1 |
| Note: | substitution is restricted |
| Note: | and tautomeric forms and mixtures and physiologically tolerated salts, hydrates and esters |
| Note: | additional oxo formation also claimed |
| Stereochemistry: | and stereoisomeric forms and mixtures |

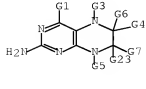
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 11 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 142:404279 MARPAT Full-text
TITLE: Use of pteridine derivatives for the treatment of increased intracranial pressure and secondary ischemia
INVENTOR(S): Doblhofer, Robert; Tegtmeier, Frank
PATENT ASSIGNEE(S): Vasopharm Biotech GmbH, Germany
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005037286 | A1 | 20050428 | WO 2003-EP3096 | 20030325 |
| W: US | | | | |
| CA 2519919 | A1 | 20041007 | CA 2003-2519919 | 20031008 |
| WO 2004084906 | A1 | 20041007 | WO 2003-EP11138 | 20031008 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003293607 | A1 | 20041018 | AU 2003-293607 | 20031008 |
| EP 1605947 | A1 | 20051221 | EP 2003-788945 | 20031008 |
| EP 1605947 | B1 | 20060802 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| CN 1758913 | A | 20060412 | CN 2003-80110211 | 20031008 |
| JP 2006514965 | T | 20060518 | JP 2004-569858 | 20031008 |
| AT 334681 | T | 20060815 | AT 2003-788945 | 20031008 |
| ES 2270151 | T3 | 20070401 | ES 2003-788945 | 20031008 |
| MX 2005PA09491 | A | 20060222 | MX 2005-PA9491 | 20050906 |
| US 20070032498 | A1 | 20070208 | US 2005-549200 | 20050916 |
| PRIORITY APPLN. INFO.: | | | WO 2003-EP3096 | 20030325 |
| | | | WO 2003-EP11138 | 20031008 |

AB The invention discloses the use of pteridine derivs. for treating increased intracranial pressure and/or secondary ischemia. Compound preparation is included.

MSTR 3



G1 = 20

G2 = alkyl <containing 1-20 C> (opt. substd.) / cycloalkyl (opt. substd.)
G4 = Ph
G5 = 30

G10 = alkyl (opt. substd. by G11)
Patent location: claim 6
Note: and physiologically tolerated salts, hydrates, and esters, and tautomers
Stereochemistry: and stereoisomers

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

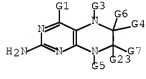
L41 ANSWER 12 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:307610 MARPAT Full-text
TITLE: Use of pteridine derivatives for the treatment of increased intracranial pressure, secondary ischemia, and disorders associated with an increased level of cytotoxic reactive oxygen species
INVENTOR(S): Doblhofer, Robert; Tegtmeier, Frank
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H., Germany
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004084906 | A1 | 20041007 | WO 2003-EP11138 | 20031008 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| WO 2005037286 | A1 | 20050428 | WO 2003-EP3096 | 20030325 |
| W: US | | | | |
| CA 2519919 | A1 | 20041007 | CA 2003-2519919 | 20031008 |
| AU 2003293607 | A1 | 20041018 | AU 2003-293607 | 20031008 |

EP 1605947 A1 20051221 EP 2003-788945 20031008
EP 1605947 B1 20060802
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
JP 2006514965 T 20060518 JP 2004-569858 20031008
MX 2005PA09491 A 20060222 MX 2005-PA9491 20050906
US 20070032498 A1 20070208 US 2005-549200 20050916
PRIORITY APPLN. INFO.: WO 2003-EP3096 20030325
WO 2003-EP11138 20031008

AB The present invention relates to the use of pteridine derivs. for the treatment of increased intracranial pressure, secondary ischemia, and disorders associated with an increased level of cytotoxic reactive oxygen species. H4-aminobiopterin (preparation given) caused a clear concentration dependent contraction of both rat basilar arteries and middle cerebral arteries.

MSTP 3




G1 = 20


G2 = alkyl <containing 1-20 C> (opt. substd.) / cycloalkyl (opt. substd.)
G4 = Ph
G5 = 30




G10 = alkyl (opt. substd. by G11)
Patent location: claim 6
Note: and physiologically tolerated salts, hydrates, and esters, and tautomers
Stereochemistry: and stereoisomers

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 13 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:260771 MARPAT Full-text

TITLE: Preparation of dihydropteridinones as anticancer agents

INVENTOR(S): Hoffmann, Matthias; Grauert, Matthias; Brandl, Trixi; Breitfelder, Steffen; Eickmeier, Christian; Steegmaier, Martin; Schnapp, Gisela; Baum, Anke; Quant, Jens Juergen; Solca, Flavio; Colbatzky, Florian

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co Kg, Germany

SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004076454 | A1 | 20040910 | WO 2003-EP1935 | 20030226 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2517020 | A1 | 20040910 | CA 2003-2517020 | 20030226 |
| AU 2003215591 | A1 | 20040917 | AU 2003-215591 | 20030226 |
| EP 1599478 | A1 | 20051130 | EP 2003-816028 | 20030226 |
| EP 1599478 | B1 | 20070509 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003018145 | A | 20060221 | BR 2003-18145 | 20030226 |
| CN 1745081 | A | 20060308 | CN 2003-826029 | 20030226 |
| JP 2006514667 | T | 20060511 | JP 2004-568646 | 20030226 |
| JP 3876265 | B2 | 20070131 | | |
| AT 361924 | T | 20070615 | AT 2003-816028 | 20030226 |
| ES 2287583 | T3 | 20071216 | ES 2003-816028 | 20030226 |
| CN 101200457 | A | 20080618 | CN 2008-10002434 | 20030226 |
| ZA 2005005668 | A | 20060329 | ZA 2005-5668 | 20050714 |
| IN 2005DN03735 | A | 20070810 | IN 2005-DN3735 | 20050823 |
| NO 2005004414 | A | 20050923 | NO 2005-4414 | 20050923 |
| JP 2006335769 | A | 20061214 | JP 2006-254000 | 20060920 |
| IN 2007DN00895 | A | 20070803 | IN 2007-DN895 | 20070202 |
| IN 2007DN01130 | A | 20070427 | IN 2007-DN1130 | 20070212 |

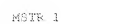
PRIORITY APPLN. INFO.:

| | |
|---|---|
| CN 2003-826029 | 20030226 |
| EP 2003-816028 | 20030226 |
| JP 2004-568646 | 20030226 |
| WO 2003-EP1935 | 20030226 |
| EP 2004-19359 | 20040814 |
| EP 2004-19366 | 20040814 |

AB Dihydropteridinones I [R1, R2 = h, alkyl; R1R2 = alkylene; R3 = H, (un)substituted alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cyclolakenyl, spirocycloalkyl, heterocyclyl; R1R3, R2R3 = alkylene, heteroalkylene; R4 = H, CN, OH, halogen, (un)substituted NH2, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl; R5 = (un)substituted morpholinyl, piperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, diketomethylpiperazinyl, sulfoxomorpholinyl, thiomorpholinyl, azacycloheptyl, (un)substituted NH2; L = alkylene,

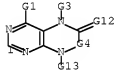
alkenylene, arylene, alkylarylene, arylalkylene, cycloalkylene, heteroarylene; n = 0, 1; m = 1, 2] were prepared for use in the treatment of cancer, infections, inflammation, and autoimmune disease. Thus, the piperazine II was obtained by amidating the acid with 1-(3-aminopropyl)-4-methylpiperazine. II had EC50 against HeLaS3 cells of 0.081 μM/L.

MSTR 1



G1 = NH2
G4 = 14

G12 = O
G13 = alkyl <containing 1-10 C> (opt. substd.)
G15 = NH
G18 = 1



Patent location: claim 1
Note: and pharmacologically acceptable acid addition salts
Note: also incorporates claims 10 and 12
Note: substitution is restricted
Stereochemistry: and tautomers, racemates, enantiomers, diastereomers and mixtures

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 14 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 138:238200 MARPAT Full-text
TITLE: Preparation of dihydropteridinones as cell proliferation inhibitors
INVENTOR(S): Hoffmann, Matthias; Grauert, Matthias; Breitfelder, Steffen; Eickmeier, Christian; Pohl, Gerald; Lehmann-Lintz, Thorsten; Redemann, Norbert; Schnapp, Gisela; Steegmaier, Martin; Bauer, Eckhart; Quant, Jens Juergen

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003020722 | A1 | 20030313 | WO 2002-EP9728 | 20020830 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 20040029885 | A1 | 20040212 | US 2002-226710 | 20020823 |
| US 6806272 | B2 | 20041019 | | |
| CA 2458699 | A1 | 20030313 | CA 2002-2458699 | 20020830 |
| AU 2002337047 | A1 | 20030318 | AU 2002-337047 | 20020830 |
| AU 2002337047 | B2 | 20080110 | | |
| EP 1427730 | A1 | 20040616 | EP 2002-772249 | 20020830 |
| EP 1427730 | B1 | 20060712 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| CN 1551881 | A | 20041201 | CN 2002-817288 | 20020830 |
| JP 2005501904 | T | 20050120 | JP 2003-524992 | 20020830 |
| JP 3876254 | B2 | 20070131 | | |
| NZ 531928 | A | 20051028 | NZ 2002-531928 | 20020830 |
| AT 332898 | T | 20060815 | AT 2002-772249 | 20020830 |
| ES 2268093 | T3 | 20070316 | ES 2002-772249 | 20020830 |
| HU 2004001293 | A3 | 20080328 | HU 2004-1293 | 20020830 |
| US 20040147524 | A1 | 20040729 | US 2004-756623 | 20040113 |
| NO 2004000680 | A | 20040216 | NO 2004-680 | 20040216 |
| ZA 2004001365 | A | 20050527 | ZA 2004-1365 | 20040219 |
| BR 2004000582 | A | 20051018 | BR 2004-582 | 20040225 |
| IN 2004DN00471 | A | 20050401 | IN 2004-DN471 | 20040226 |
| MX 2004PA02067 | A | 20040607 | MX 2004-PA2067 | 20040303 |
| IN 2007DN00894 | A | 20070803 | IN 2007-DN894 | 20070202 |

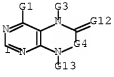
PRIORITY APPLN. INFO.: DE 2001-10143272 20010904
US 2001-332681P 20011114
US 2002-226710 20020823
WO 2002-EP9728 20020830
EP 2004-19365 20040814

AB Title compds. I [R1 = H, NH2, XH, etc.; R2 = H, CHO, XH; R3, R4 = (un)substituted alkyl, alkenyl, alkynyl, etc.; R5 = H, (un)substituted alkyl, alkenyl, etc.; R6 = (un)substituted aryl, heteroaryl; R7 = H, CO-X-alkyl; X = O, S] and their pharmaceutically acceptable salts were prepared For example, coupling of benzoic acid II, i.e., prepared from 2,4-dichloro-5-nitropyrimidine in 4-steps, and benzylamine afforded dihydropteridinone III. Compds. I are claimed useful as anti-inflammatory, anti-infective and antitumor agents.

MSTR 1

G1 = NH2
G4 = 14

G12 = O
G13 = alkyl <containing 1-10 C> (opt. substd.)
G15 = NH
G18 = 1



Patent location: claim 1
Note: and pharmacologically acceptable acid addition salts
Note: also incorporates claims 10 and 12
Note: substitution is restricted
Stereochemistry: and tautomers, racemates, enantiomers, diastereomers and mixtures

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 15 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 134:237499 MARPAT Full-text
TITLE: Preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for use as pharmaceuticals
INVENTOR(S): Pfleiderer, Wolfgang; Schmidt, Harald; Froehlich, Lothar; Kotsonis, Peter; Taghavi-Moghadam, Shahriyar
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001021619 | A1 | 20010329 | WO 2000-EP8833 | 20000911 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| DE 19944767 | A1 | 20010329 | DE 1999-19944767 | 19990917 | |
| EP 1216246 | A1 | 20020626 | EP 2000-964154 | 20000911 | |
| EP 1216246 | B1 | 20050824 | | | |

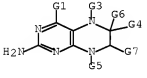
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

| | | | | |
|---|---|---|---|---|
| JP 2004522690 | T | 20040729 | JP 2001-524995 | 20000911 |
| AT 302778 | T | 20050915 | AT 2000-964154 | 20000911 |
| ES 2248124 | T3 | 20060316 | ES 2000-964154 | 20000911 |
| US 6844343 | B1 | 20050118 | US 2002-70976 | 20020719 |

PRIORITY APPLN. INFO.: DE 1999-19944767 19990917
WO 2000-EP8833 20000911

AB Pteridines, such as I [R1, R2 = H, alkyl, aryl, arylalkyl; R1R2 = nitrogen bound heterocyclyl, such as 1-piperidinyl or 4-morpholinyl; R4 = alkyl, alkenyl, alkynyl, cycloalkenyl, aryl, etc.; R3, R5 = acyl, aroyl, R6 = R7 = H, or R3R6 = R5R7 = bond;], were prepared for pharmaceutical use. Thus, pteridine II was prepared via cyclocondensation of N4,N4-dimethylpyrimidinetetramine dihydrochloride and phenylglyoxal monoxime. The prepared pteridines were tested for nitric oxide synthase inhibiting activity.

MSTR 1




G1 = 20


G4 = Ph
G5 = 30


G10 = alkyl (opt. substd. by G11)

Patent location: claim 1
Note: and physiologically useful salts, hydrates, and esters
Stereochemistry: and stereoisomers and tautomers

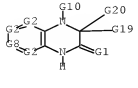
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 16 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 132:78568 MARPAT Full-text
TITLE: Preparation of substituted quinoxalin-2(1H)-ones useful as HIV reverse transcriptase inhibitors
INVENTOR(S): Patel, Mona; Mchugh, Robert Joseph
PATENT ASSIGNEE(S): Du Pont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000000478 | A1 | 20000106 | WO 1999-US14395 | 19990625 |
| W: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2334332 | A1 | 20000106 | CA 1999-2334332 | 19990625 |
| AU 9947196 | A | 20000117 | AU 1999-47196 | 19990625 |
| EP 1089979 | A1 | 20010411 | EP 1999-930715 | 19990625 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO | | | | |
| PRIORITY APPLN. INFO.: | | | US 1998-90893P | 19980626 |
| | | | US 1998-90893 | 19980626 |
| | | | WO 1999-US14395 | 19990625 |

AB The title compds. [I; A = O, S; W = N, CR3; X = N, CR4; Y = N, CR5; Z = N, CR6; C = cyclopropyl, C1-3 alkyl substituted with 3-7 halogens; provided that the number of W, X, Y, and Z which are N, is 0-2; R1 = CO2R12, COR12, SO2R12, etc.; R2 = CH:CR7R8, C.tplbond.CR8, CH:CHCHR7R8, etc.; R3 = H, F, Cl, etc.; R4 = H, F, Cl, etc.; R5 = H, F, Cl, etc.; R6 = H, OH, F, etc.; R7 = H, Me, Et, etc.; R8 = H, F, haloalkyl, etc.; R12 = alkyl, alkenyl, alkynyl, etc.; provided, if simultaneously, each of W, X, Y, and Z are carbon, then R2 is not unsubstituted alkyl], which are useful as inhibitors of HIV reverse transcriptase, were prepared and formulated. E.g. a multi-step synthesis of I [W = X = Y = Z = CH; A = O; C = CF3; R1 = cyclopropylmethyl; R2 = cyclopropylethynyl, etc.] was given. Compds. I have been found to have an IC50 of < 60 μM in HIV-1 RT assay.

M3TR 1



G1 = O
G2 = N / 13



G3 = NH2
G8 = N
G10 = 56



G16 = carbon chain <containing 1 or more C,
0-1 double bond, 0-1 triple bond>
G19 = alkyl <containing 1-3 C> (substd. by (3-7) G18)
G20 = 67

G21 = carbon chain <containing 1 or more C,
0-1 double bond, 0-1 triple bond>
Derivative: or pharmaceutically acceptable salts
Patent location: claim 1
Note: additional ring formation also claimed
Note: substitution is restricted
Stereochemistry: or stereoisomers

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 17 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 121:300922 MARPAT Full-text
TITLE: Preparation of azaquinoxalinones as antiviral agents
INVENTOR(S): Billhardt-Troughton, Uta Maria; Roesner, Manfred; Bender, Rudolf; Meichsner, Christoph
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Eur. Pat. Appl., 42 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

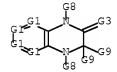
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 590428 | A1 | 19940406 | EP 1993-114934 | 19930916 |
| EP 590428 | B1 | 19991215 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| AT 187724 | T | 20000115 | AT 1993-114934 | 19930916 |

| | | | | | |
|---|---|---|---|---|---|
| ES 2141744 | T3 | 20000401 | ES 1993-114934 | 19930916 | |
| AU 9347553 | A | 19940331 | AU 1993-47553 | 19930923 | |
| AU 664643 | B2 | 19951123 | | | |
| US 5424311 | A | 19950613 | US 1993-125163 | 19930923 | |
| IL 107081 | A | 19990714 | IL 1993-107081 | 19930923 | |
| CA 2106882 | A1 | 19940327 | CA 1993-2106882 | 19930924 | |
| CA 2106882 | C | 20070417 | | | |
| ZA 9307081 | A | 19940418 | ZA 1993-7081 | 19930924 | |
| HU 65302 | A2 | 19940502 | HU 1993-2696 | 19930924 | |
| JP 06211855 | A | 19940802 | JP 1993-237679 | 19930924 | |
| GR 3032520 | T3 | 20000531 | GR 2000-400216 | 20000131 | |

PRIORITY APPLN. INFO.: DE 1992-4232392 19920926

AB Title compds. [tautomeric I; R1 = halo, CF3, OH, (cyclo)alkyl, alkoxy, Ph, etc.; R2,R5 = H, OH, alkyl, etc.; R3,R4 = H, (cyclo)alk(en)yl, (hetero)aryl, etc.; V,W,Y,Z = CH, CR1, N; X = O, S, NR2; n = 0-3] were prepared Thus, 2,6-dichloro-3-nitropyridine was condensed with L-H2NCHMeCO2Me and the reduced monocondensed product cyclized to give title compound (S)-II (R5 = H) which was reductively condensed with Me2CH:CHCHO to give (S)-II (R5 = CH2CH:CHMe2). The latter had MIC of 0.08μg/mL against HIV in cell culture.

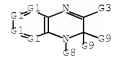
MSTR 1



G1 = (1-2) N / 11

G2 = NH2
G3 = O
G8 = alkynyl (opt. substd.)
Patent location: claim 1
Note: substitution is restricted

MSTR 2



G1 = (1-2) N / 11

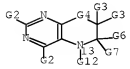
G2 = NH2
G3 = OH
G8 = alkynyl (opt. substd.)
Patent location: claim 1
Note: substitution is restricted

L41 ANSWER 18 OF 18 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 116:83686 MARPAT Full-text
TITLE: Preparation of pyrimidothiazines as muscle relaxants
INVENTOR(S): Senaga, Masahiro; Sugimoto, Hachiro; Suzuki, Takeshi; Kajiwara, Shoji; Ueno, Koji; Higure, Kunizo; Nagato, Satoru; Yoshida, Ichiro; Tanaka, Kazuo; Et, Al.
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 43 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 03118380 | A | 19910520 | JP 1989-254348 | 19890929 |
| JP 2886570 | B2 | 19990426 | | |
| PRIORITY APPLN. INFO.: | | | JP 1989-254348 | 19890929 |

AB The title compds. I [A1, A2 = CH, N; at least one of A1 and A2 is N; R1 = H, OH, alkoxy, NR4R5, etc.; R4, R5 = H, alkyl; R2, R3 = H, alkyl, aryl, etc.; W = SOpNR6, etc.; R6 = H, alkyl; p = 0-2; B = CH2, CO; E = H, Q1; u = 0, 1; X = (CH2)n, (CH2)mCO; m, n = 2-8; Y, Z = N, CR8; R8 = H, OH; r, s = 1-3; R7 = H, alkyl, etc.] were prepared Reaction of thiazine II (T = Br) with N-(2-methoxybenzyl)piperazine in DMF containing Et3N, followed by workup and treatment with HCl, gave II.2HCl (T = Q2), which exhibited a min. ED of 0.1 mg/kg i.v. against contracture in rats.

MSTR 1E



G2 = NH2
G4 = 40

G5 = loweralkyl
G6 +G7 = O
Derivative: and pharmacologically acceptable salts
Patent location: claim 1

# Search History

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     FILE 'REGISTRY' ENTERED AT 17:15:12 ON 25 AUG 2008
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                3218-02-8/BI OR 51471-45-5/BI OR 60-12-8/BI OR 6036-64-2/BI OR
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                858127-59-0/BI OR 858127-60-3/BI OR 858127-61-4/BI)
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L4           50 SEA SSS SAM L3
L5         4906 SEA SSS FUL L3

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L6         18880 SEA ABB=ON  PLU=ON  L5
L7              STRUCTURE UPLOADED
                S L7

     FILE 'REGISTRY' ENTERED AT 17:17:41 ON 25 AUG 2008
L8           50 SEA SUB=L5 SSS SAM L7

     FILE 'HCAPLUS' ENTERED AT 17:17:42 ON 25 AUG 2008
L9           57 SEA ABB=ON  PLU=ON  L8

     FILE 'REGISTRY' ENTERED AT 17:17:44 ON 25 AUG 2008
L10          50 SEA SUB=L5 SSS SAM L7

     FILE 'REGISTRY' ENTERED AT 17:26:21 ON 25 AUG 2008
L11             STRUCTURE UPLOADED
L12          50 SEA SUB=L5 SSS SAM L11
L13             STRUCTURE UPLOADED
L14           5 SEA SUB=L5 SSS SAM L13
L15          74 SEA SUB=L5 SSS FUL L13

     FILE 'HCAPLUS' ENTERED AT 17:30:32 ON 25 AUG 2008
L16         113 SEA ABB=ON  PLU=ON  L15
L17         107 SEA ABB=ON  PLU=ON  L16 AND (PRY<=2003 OR AY<=2003 OR PY<=2003)

L18           4 SEA ABB=ON  PLU=ON  DOBLHOFER R?/AU
L19          56 SEA ABB=ON  PLU=ON  TEGTMEIER F?/AU
L20          57 SEA ABB=ON  PLU=ON  (L18 OR L19)
L21           3 SEA ABB=ON  PLU=ON  L20 AND L17

     FILE 'REGISTRY' ENTERED AT 17:32:41 ON 25 AUG 2008
L22             STRUCTURE UPLOADED
L23           0 SEA SUB=L5 SSS SAM L22
L24           4 SEA SUB=L5 SSS FUL L22
L25           1 SEA ABB=ON  PLU=ON  L24 AND L2

     FILE 'HCAPLUS' ENTERED AT 17:34:15 ON 25 AUG 2008
L26           3 SEA ABB=ON  PLU=ON  L24

     FILE 'REGISTRY' ENTERED AT 17:35:08 ON 25 AUG 2008
L27             STRUCTURE UPLOADED
L28           0 SEA SUB=L5 SSS SAM L27
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L29             6 SEA SUB=L5 SSS FUL L27

     FILE 'HCAPLUS' ENTERED AT 17:35:46 ON 25 AUG 2008
L30             4 SEA ABB=ON  PLU=ON  L29

     FILE 'WPIX' ENTERED AT 17:36:45 ON 25 AUG 2008
L31             0 SEA SSS SAM L27
L32             0 SEA SSS FUL L27

     FILE 'BEILSTEIN' ENTERED AT 17:37:57 ON 25 AUG 2008
L33             5 SEA ABB=ON  PLU=ON  L29
L34             5 SEA ABB=ON  PLU=ON  L29
L35             1 SEA ABB=ON  PLU=ON  L34 AND BABSAN/FA
                  SEL BABSAN

     FILE 'BABS' ENTERED AT 17:38:31 ON 25 AUG 2008
L36             1 SEA ABB=ON  PLU=ON  5617307/BABSAN

     FILE 'BEILSTEIN' ENTERED AT 17:38:48 ON 25 AUG 2008
L37             4 SEA ABB=ON  PLU=ON  L34 NOT L35

     FILE 'MARPAT' ENTERED AT 17:39:42 ON 25 AUG 2008
L38             1 SEA SSS SAM L27
L39            11 SEA SSS FUL L27

     FILE 'HCAPLUS' ENTERED AT 17:41:13 ON 25 AUG 2008
                  D STAT QUE L30
L40             3 SEA ABB=ON  PLU=ON  L30 NOT L21

     FILE 'HCAPLUS, BEILSTEIN, BABS, MARPAT' ENTERED AT 17:42:30 ON 25 AUG 2008
L41            18 DUP REM L40 L32 L37 L36 L39 (1 DUPLICATE REMOVED)
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